REMARKS/ARGUMENTS

Claims 20, 21, 28 to 35, 37, 41, 42, 46, 52 to 56 and 59 to 64 are pending in the application. The Title has been amended to more accurately reflect the claimed invention. See, for example, currently pending claim 20. Claims 21, 28 to 31, 34, 35, 37, 59 and 60 have been amended to make the claims more clear. Addition of "G-CSF, erythropoietin, GM-CSF" to claims 29 and 37 is supported, for example, at page 31, lines 6 to 8 of the specification. New claims 62 to 64 have been added and are supported, for example, at page 31, lines 2, 6 and 7 of the specification. Claim 60 has been amended to avoid redundancy with new claim 62. This amendment includes no new matter.

The Examiner rejects claims 20, 21, 28 to 35, 37, 41, 42, 46, 52 to 56 and 59 to 61 under 35 USC 112, first paragraph, as failing to comply with the written description requirement stating that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicant traverses the rejection.

The Examiner states in the second and third full paragraphs at page three of the Office action mailed May 15, 2007, that analyzing whether the written description requirement is met for the claimed invention it must be first determined whether a sufficient description of a representative number of species have been described by structure and function, i.e., have the phenotypic consequences of altering the genotype been described. The Examiner also states that "At best the specification as filed discloses the making of chimeric chickens by transducing stage X embryos with NLB-CMV-BL (ALV-based vector) transduction particles (spec page 32, example-3, page 33 lines 3-9). Even though the specification as filed teaches the production of b-lactamase in egg white the specification fails to disclose any germ line transgenic avian (even a chicken) whose egg contains any exogenous protein produced (to be purified) by any transgene (which is not limited to a particular structure) present in the germ line of the transgenic avian and wherein the exogenous protein is produced in the transgenic oviduct." The Examiner continues, citing Brenner v Manson, 383 US 519, 536, 148 USPQ 689, 696 (1966), stating that, therefore, the limited disclosure in the specification is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the huge genera recited in the claims at the time of filing and that patent protection is not granted in return for vague intimations of general ideas that may or may not be workable. Applicant disagrees with the Examiner's conclusions.

The application as filed provides details of how to practice a predictable and workable method for producing germ-line transgenic avians. These germline transgenic avians have the phenotype of producing specific exogenous proteins (examples of which are provided at page 31 of the specification) in their oviduct and laying eggs containing the exogenous proteins.

Data detailing the production of G0 germline transgenic chickens containing the β-lactamase transgene is presented in the application (e.g., Examples 1 to 3 of the application). Data proving that the β-lactamase transgene of some of these germline transgenic G0 birds is passed through the germline is presented at paragraph 5 of the Declaration of Robert D Ivarie (Ivarie Declaration), a copy of which is filed herewith, where it is stated that:

> Germline transgenic chickens that produce beta lactamase (BL) in their oviduct were made in accordance with the Application. The data for the production of BL germline transgenic birds is as follows: Production of G0 chimeric germline transgenic NLB-CMV-BL chickens was described in Examples 1 to 3 of the Application. G1 germline transgenic birds that produce BL in the oviduct were produced from the chimeric germline transgenic G0 male bird having the highest level of transgene in the sperm using standard breeding methodologies apparent to practitioners of ordinary skill in the art, i.e., G0 roosters containing transgene in their sperm were crossed with non-transgenic chickens. Out of a total of 1026 G1 offspring tested by PCR analysis of genomic DNA, one rooster and two hens tested positive for the NLB-CMV-BL transgene. Eggs laid by the G1 germline transgenic females and their descendents contained between about 0.5 μg/ml and about 1.6 μg/ml of BL, as determined by ELISA.

As stated by Dr. Ivarie, the germline transgenic G1 birds were produced from the G0 β-lactamase birds using standard breeding methodologies apparent to practitioners of skill in the art, i.e., G0 roosters containing transgene in their sperm were crossed with non-transgenic chickens. In addition, Example 10 of the Application entitled "Production of Fully Transgenic G1 Chickens" specifically contemplates production of fully transgenic G1 birds and discusses a specific breeding methodology which involves crossing transgenic G0 birds with non-transgenic birds to obtain the fully transgenic G1 birds.

Numerous examples of specific proteins are provided in the specification which can be produced in accordance with the present invention, the coding sequences of which were well known in the art prior to the filing of the application. See, for example, page 30, line 30, to page 31, line 11, which includes a number of examples of proteins that may be produced in

accordance with the invention. In addition, germline transgenic birds have been made in accordance with the invention that produce β-lactamase, interferon alpha 2, G-CSF and erythropoietin. As can be seen in paragraphs 6 to 9 of the Ivarie Declaration, the production of each of these proteins was accomplished using the same methods described in the present application as filed. That is, the β-lactamase coding sequence of the NLB vector used for production of β-lactamase was replaced with coding sequences for each of the following: G-CSF, erythropoietin and interferon (i.e., interferon alpha 2). Germline transgenic chickens expressing each of these proteins in the oviduct were produced using these NLB vectors in accordance with the application. It is noted here that the line of erythropoietin producing avians referred to in the Ivarie Declaration is not the same line of erythropoietin producing avians disclosed in Example 11 of US Patent No. 7,129,390, in which an NLB-MDOT-EPO vector is used.

Applicant has presented multiple examples of lines of germline transgenic birds that lay eggs containing exogenous protein which were produced in accordance with the application. In addition, it is stated in paragraph 4 of the Ivarie Declaration that "by following the disclosure of the Application, a practitioner of ordinary skill in the art would be able to make lines of germline transgenic avians that lay eggs containing many different proteins in addition to those proteins that have been produced thus far and in addition to those proteins disclosed in the Application". Therefore, since applicant has shown that the application as filed presented sufficient written description to enable members of the public to understand and carry out the invention producing a variety of exogenous proteins, the rejection should be withdrawn.

The Examiner states at the first full paragraph of page 3 of the Office action mailed 5/15/07 that "The scope of transgenic avian, which lay eggs containing an exogenous protein of interest encompasses any transgenic avian (across class avis) which lays eggs containing any exogenous protein of interest". Therefore, it appears the Examiner is contending that the present invention may be limited to a certain class of birds such as chickens. Applicant disagrees with this contention.

It is expected that the methods of the invention would work in a number of avians other than chickens since the avian leucosis virus (from which NLB is derived), as the name implies, is not limited to infection of chickens. As stated in paragraph 12 of the Ivarie Declaration "the infectivity of ALV is not limited to chickens". In addition, paragraphs 13 and 14 of the Ivarie Declaration provide specific support for the production of transgenic quail which lay eggs

containing exogenous protein (G-CSF) using the methods of the Application. Though no screening was done to identify G1 transgenic quail, it is clearly stated at the end of paragraph 14 of the Ivarie Declaration that "I believe with a high level of certainty that G1 germline transgenic quail which produce exogenous protein in the oviduct could be obtained from the transgenic G0 quails that were produced." Paragraph 14 of the Ivarie Declaration also states that "I believe germline transgenic avians other than chicken and quail which produce exogenous protein in the oviduct can be produced in accordance with the invention as disclosed in the Application." Therefore, since the methods of the application can be used to produce germline transgenic avians other than chickens which lay eggs containing exogenous protein, the rejection should be withdrawn.

The Examiner rejects claims 20, 21, 28 to 35, 37, 41, 42, 46, 52 to 56 and 59 to 61 under 35 USC 112, first paragraph as failing to comply with the enablement requirement stating that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner states that since the specification fails to disclose the making of any germ line transgenic avian (even a chicken) whose egg contains any exogenous protein produced (to be purified) it is unclear how one skilled in the art can use the invention and that undue experimentation is required to practice the invention. The Examiner also states that making a germline transgenic avian capable of producing eggs containing an exogenous protein of interest using any transgene construct not oviduct tissue specific is not considered routine in the art. In addition, the Examiner states that "The state of the art at the time of filing regarding making germ-line transgenic birds that produce an exogenous protein of interest in the eggs is considered highly unpredictable especially in view of low transgene transmission to the progeny". The Examiner also states that random integration of the viral vectors into the genome can render tissue specificity highly unpredictable. Applicant traverses the rejection.

Applicant first notes that as far as the state of the art regarding making germ-line transgenic birds that produce an exogenous protein of interest in their eggs, such a working technology was unknown in the field prior to the filing of the present application. See, for example, the last sentence of paragraph 7 of the Gibbins Declaration filed with applicant's Response of September 18, 2006 which states that "I am unaware of any work pre-dating

October 18, 1998 (filing date for US Patent No. 6,730,882) that led to the deposition of heterologous protein in the egg of a transgenic avian."

Applicant has provided disclosure in the application as filed which allowed a practitioner of skill in the art, at the time of filing, to produce germline transgenic avians which lay eggs containing a variety of exogenous proteins with predictability and without undue experimentation. As Dr. Ivarie states in paragraph 4 of his Declaration:

> the methods disclosed in the Application have proven to be robust and reliable enabling us to successfully make germline transgenic birds which lay eggs containing a number of proteins specifically named in the Application (for example, at page 31 of the Application) including: β-lactamase, granulocyte colony stimulating factor (G-CSF), erythropoietin (EPO) and interferon, i.e., interferon alpha 2 (IFNα2). Furthermore, by following the disclosure of the Application, a practitioner of ordinary skill in the art would be able to make lines of germline transgenic avians that lay eggs containing many different proteins in addition to those proteins that have been produced thus far and in addition to those proteins disclosed in the Application.

Though routine repetition may be required to identify G1 transgenic avians in accordance with the invention, such repetitive work does not qualify as undue experimentation. As stated in paragraph 10 of the Ivarie Declaration "As is expected a number of transgenic birds typically need to be screened in order to identify the transgenic G1 offspring (first generation of fully transgenic germline birds) obtained from the germline chimeras. However, such screening and identification can be accomplished routinely and with predictability by skilled technicians in the field of poultry science and molecular biology." In addition, random integration of the vector employed in the invention and use of a non-tissue specific promoter have not led to unpredictability. As stated in paragraph 10 of the Ivarie Declaration "identifying lines of G1 birds which lay eggs containing useful quantities of the transgene encoded exogenous protein has been predictable and routine using vectors of the invention." Dr. Ivarie continues stating: "For example, use of the non-tissue specific CMV promoter to express the exogenous protein in the avian oviduct has been routine and has not required undue experimentation. In addition, random integration of the NLB vector into the avian genome has not made practicing the invention unpredictable and has not imposed undue experimentation in order to practice the invention." Furthermore, production in accordance with the application of four examples of germline

transgenic avians that lay eggs containing exogenous proteins are described in paragraphs 5 to 9 of the Ivarie Declaration.

Three of the four examples of germline transgenic avians that lay eggs containing exogenous proteins discussed in the Ivarie Declaration lay eggs containing the pharmaceutical or therapeutic proteins, i.e., EPO, G-CSF and interferon, i.e., interferon alpha 2. As is understood by a practitioner of ordinary skill, therapeutic proteins produced in accordance with the invention will be useful as pharmaceuticals after being removed (purified) from the egg white. As stated in the last sentence of each of paragraphs 7 to 9 of the Ivarie Declaration: purification of exogenous proteins such as IFNα2, G-CSF and EPO from eggs laid by transgenic birds can readily be accomplished by a practitioner of ordinary skill in the art using standard protein purification methodologies. Furthermore, IFNα2, G-CSF and EPO have in fact been purified from eggs, as stated in paragraphs 7 to 9 of the Ivarie Declaration. It is also significant that, as stated in paragraph 6 and paragraph 7 of the Ivarie Declaration, both purified interferon alpha 2 and purified G-CSF produced in accordance with the invention have entered clinical trials for FDA regulatory approval.

Therefore, applicant requests that the enablement rejection be withdrawn since the disclosure of the Application in combination with the knowledge of a practitioner of ordinary skill in the art provides for the making and using of the claimed invention.

The Examiner has made obviousness type double patenting rejections over the claims of copending patent application Nos. 11/377,302; 11/274,674; 11/100,255; 11/099,934; 11/337,361; and 11/376,023. The Examiner indicates that these rejections are provisional rejections since the conflicting claims have not yet been patented.

MPEP §822.01 states that "If the 'provisional' double patenting rejections in both applications are the only rejections remaining in those applications, the examiner should then withdraw that rejection in one of the applications and permit the application to issue as a patent....". None of the cited co-pending applications have been allowed. Therefore, applicant respectfully requests that the Examiner withdraw the provisional double patenting rejection and allow the pending claims in the present application to issue.

Should any one of the cited co-pending applications issue before the allowance of the present application, applicant is willing to consider the possibility of filing an appropriate terminal disclaimer.

In sum, applicant has shown that claims 20, 21, 28 to 35, 37, 41, 42, 46, 52 to 56 and 59 to 64 comply with the requirements for patentability and are allowable. If any issues remain to be addressed in this matter, which might be resolved by discussion, the Examiner is respectfully requested to call applicant's undersigned counsel at the number indicated below.

Respectfully submitted,

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